International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 08-11-2018; Accepted: 10-12-2018
www.medicalsciencejournal.com
Volume 5; Issue 1; January 2019; Page No. 44-48

Vitamin D deficiency and coronary artery disease

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Abstract
Sunlight is a rich source of Vitamin D (Vit D) that prevents us from numerous ailments such as autoimmune disorders, various types of cancer, and the above all cardiovascular diseases (CVD). Growing evidence has shown a strong association between vitamin D deficiency and hypertension, metabolic syndrome, diabetes mellitus and atherosclerosis. The mechanisms by which vitamin D exerts its cardiovascular protective effects are still not completely understood, but there is evidence that it participates in the regulation of renin-angiotensin system and the mechanisms of insulin sensitivity and activity of inflammatory cytokines, besides its direct cardiovascular actions. Several studies linking vitamin D deficiency with cardiometabolic risk as well as small randomized trials that have evaluated the cardiovascular effects of its supplementation are presented. However, large randomized placebo-controlled studies are still needed before we can definitively establish the role of vitamin D supplementation in the prevention and control of cardiovascular disease.

Aims and Objectives: The aim of the present paper was to review the most important mechanisms explaining the possible association of vitamin D deficiency and cardiovascular diseases, Vitamin D deficiency is a prevalent condition in many countries. The aim of this study is to elucidate whether deficient vitamin D status is associated with coronary artery disease considering cardiovascular risk factors.

Material and Methods: We measured 50 (OH) D serum levels in 100 patients that were diagnosed with clinically diagnosed coronary artery disease and 50 individuals in the control group who were matched for age and sex with the patients and examined the association between serum 25 (OH) D and coronary artery disease with regard to cardiovascular risk factors.

Conclusion: Patients without significant lesions in coronary arteries presented the highest 25(OH)D level, significantly higher than patients with one-, two-, and three-vessel coronary artery disease (CAD) ($p < 0.01$). Significantly lower level of the 25(OH) D was observed in patients hospitalized due to acute coronary syndrome (ACS) in comparison to patients hospitalized due to stable CAD ($p < 0.001$). Lower 25(OH) D levels were observed in patients with the history of myocardial infarction (MI) in comparison to patients without previous MI ($p < 0.001$). In cardiac patients with diabetes, the higher number of stenotic coronary arteries is associated with lower values of the 25(OH) D. A group of male cardiac patients with diabetes with significant stenosis in three coronary arteries, hospitalized due to acute coronary syndrome, with a history of previous MI and hyperlipidemia presented the lowest vitamin D level.

Keywords: vitamin D (Vit D), cardiac patients, acute coronary syndrome, stenosis, cardiovascular, hypertension

1. Introduction

Although the role of traditional risk factors is already consolidated, it is known that they cannot fully explain the development of CVD, which has caused continuous search for new risk factors. Growing evidence, obtained in recent years, has suggested that vitamin D deficiency may be associated with an increased risk of CVD [2]. Vitamin D is actually a steroid hormone whose primary function is the regulation of calcium and phosphorus homeostasis, through its interaction with parathyroid gland, the kidneys and intestines. Although it can be obtained through food intake, the main source of vitamin D is represented by its synthesis in the body itself [2]. Under normal conditions only about 10% of the vitamin D needed by the body is achieved by ingestion of food, both in the form of vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Thus, the main source of vitamin D is represented by its synthesis in the body itself, which begins in the skin. When exposed to ultraviolet radiation, the skin vitamin D precursor 7-dehydrocholesterol undergoes a photochemical cleavage, yielding the previtamin D3. Such labile molecule, in a 48 hour period, undergoes a molecular rearrangement resulting in the formation of vitamin D3. Both the vitamin D coming from the diet, *via* intestinal absorption, and that formed from the previtamin D3 in the skin bind to circulating proteins and are transported to the liver where it is hydroxylated at the carbon 25, giving the 25-hydroxyvitamin D3 [25(OH)D]. This is then hydroxylated again, this time at carbon 1, at mitochondrial level in cells of the proximal convoluted tubules, as well as possibly in many other tissues, under the action of 1α-hydroxylase enzyme (1α-OHase), finally yielding the 1,25-dihydroxyvitamin D3 [1,25(OH)2D], its biologically active form (Fig.). this phase activation is tightly regulated by the serum levels of PTH, calcium and phosphorus. The definition of vitamin D deficiency has also been a matter of debate. However, most agree that serum 25 (OH) D<2 0 ng/ml (or 50 nmol/l) is indicative of deficiency, in the range 20-30 ng/ml (or 50 to 75 nmol/l) match insufficiency and >30 ng/ml (or 75 nmol/l) represents vitamin D sufficiency [6]. Several factors can interfere with the prevalence of hypovitaminosis D. Less sunlight exposure that characterizes modern life in cities, coupled with the widespread use of sunscreen, stimulated by the fear of skin cancer, is undoubtedly the most important factor to the increasing prevalence of vitamin D deficiency in the world. In the study Ludwigshafen Cardiovascular Health and Risk

(LURIC), where 3,316 patients referred for a coronary angiogram were followed for seven years, it was evidenced that lower levels of both 25(OH)D and 1,25(OH)2D were independent predictors of fatal cerebrovascular accident (CVA) [13]. A similar result was obtained in the Copenhagen City Heart Study, a cohort that followed 10,170 individuals in a general population over 21 years, which also showed a clear independent inverse association between serum 25(OH) D and incidence of ischemic stroke [14].

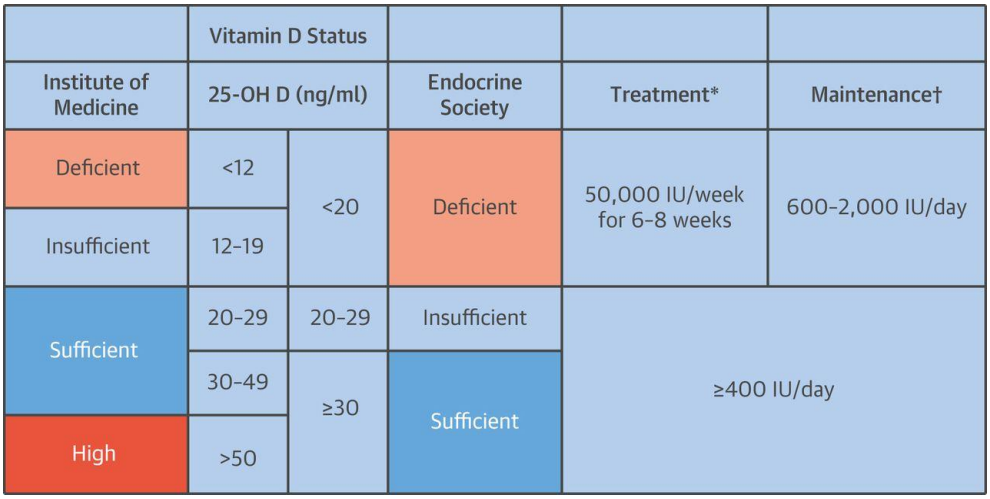

Fig 1: Vitamin D and Cardiovascular Disease

2. Material and Methods

50 patients that were diagnosed with coronary artery disease upon coronary angiography and 50 individuals in the control group who were matched for age and sex with the patients and examined the association between serum 25 (OH) D and coronary artery disease with regard to cardiovascular risk factors. The cases were selected by convenient sampling method from the patients over 40 years admitted to the hospital with the diagnosis of angina pectoris and whom the existence of coronary artery disease had been proved upon angiography. The control group was family or friends of the patients which were matched with them for sex and age and didn't have any history of angina pectoris upon clinical evaluation. The exclusion criteria of the study were unwillingness to cooperate or chronic renal diseases. Written consent was obtained from the participants. Study variables including age, sex, and education, smoking status, usage of antihyperlipidemic, antidiabetic and antihypertensive drugs were gathered through checklist. The Level of physical activity was collected by a standard questionnaire (Rapid assessment physical activity questionnaire). All the participant were subjected to following investigation: complete blood count (CBC), fasting plasma sugar, post prandial plasma sugar (2 hour after 75gm of oral glucose), glycosylated haemoglobin (HbA1c), kidney function test (KFT) (serum urea and creatinine), liver function test (LFT) (serum bilirubin, albumin, SGOT, SGPT and alkaline phosphatase), 24 hour urinary protein, serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), fasting 25-hyroxyvitamin D (25(OH)D) and ultrasound whole abdomen, 12 lead electrocardiogram, treadmill test, echocardiography and coronary angiography (CAG) (if ECG and TMT were inconclusive). Vitamin D level was measured in the form of 25-hyroxyvitamin D (25(OH) D). Patients with 25-hyroxyvitamin D level 200mg/dl or HbA1c >6.5% or on antidiabetic drugs. 25-hyroxyvitamin D was estimated by Seimen's chemiluminescent immunoassay method. LFT, KFT, and plasma Sugar were estimated using Seimen's clinical chemistry analyzer. Direct estimation of TC, HDL-C levels and TG were done using Beckman's clinical chemistry analyzer. Low and very low density lipoprotein cholesterols (LDL-C and VLDL-C) were calculated.

Table 1: Preliminary Character of participants

Age		Case%	Control%	p-value
Male	30			0.786
Female	20			
Family History of CAD	-	35.98	71.87	32.54
History of Smoking	-	30.87	14	<0.002
Physical Activity	-	24.87	16	21.23
Diabetes	-	40.98	19.22	-
Hypertension	-	26.76	17.87	0.001
Total Cholesterol	-	250±56.32		0.004
Raised Cholesterol	-	40	11.65	0.001
Obesity	-	21	34.72	0.065
Value of Vit.D	-	21±54	12±67	0.001
Deficiency of Vit.D	-	25	69	0.001

Table 2: Association of CAD with various risk factors

Variables	Odds Ratio (90% CI)	P-Value
Age	1.020 (0.979-1.057)	0.453
Sex	0.869 (0.54-.87)	0.879
Family History	2.87 (1.46-4.98)	0.005
Smoking	9.98 (4.76-4.01)	0.002
Physical activity	0.87 (0.239-0.298)	0.001
Hypertension	3.45 (2.87-3.32)	0.005
Hypercholesterolemia	6.98 (3.76-8.98)	0.002
Diabetes	3.87 (1.87-2.01)	0.001
Obesity	3.76 (2.98-5.98)	0.561
Vitamin D	1.32 (0.67-0.98)	0.005
Deficiency of Vit. D	4.98 90 (3.67-7.98)	0.002

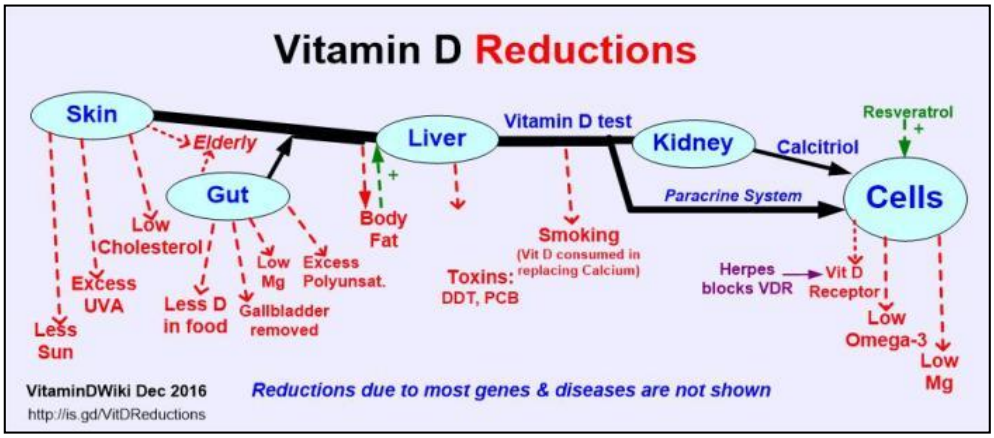

Fig 2: Schematic Representation of VIT. D Reduction

3. Results

Out of 50 patients in case group 30 were male and in control group out of 30 participants were male. Mean age was 51.23 and 66.45 year in case and control group respectively. Baseline characteristics of participants are shown in Table 1. Baseline characteristics of participants are shown in Table 1. Hypertension, diabetes, smoking, obesity, high blood cholesterol and also the amount of physical activity was significantly different between the patients and the control group (P<0.05). 25-hyroxyvitamin D level and proportion of 25-hyroxyvitamin D deficient individuals in both group have been shown in Figure. Proportion of vitamin D deficient individuals were significantly higher in the coronary artery disease group than control (P<0.05). Mean 25-hyroxyvitamin D level was also significantly lower in patients with CAD as compared to control (p<0.001). Relationship between risk factors and CAD has been shown in Table 2 as unadjusted or crude odds ratio or univariate regression analysis reveals crude odds ratio for the association between CAD and vitamin D deficiency as 3.2. Result of Multivariate regression analysis is shown in Table 3. After adjusting confounders with multivariate regression analysis, it was found that CAD is 2.7 times more common in Vitamin D deficient individual as compared to those with normal vitamin D level (p-value<0.02). Forest plot for adjusted odds ratio of each risk factors for coronary artery diseases has been shown in Figure.

Table 3: Regression analysis for association of coronary artery disease with various risk factors

Variables	**Model 1**		**Model 2**	**p-value**
Variables	Odds ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Family History	4.87 (1.76-1.98)	0.008	4.26(1.65-1.78)	0.006
Smoking	7.67(3.12-4.98)	0.001	8.01(4.76-5.32)	0.001
Physical activity	0.87(0.342-0.765)	0.002	0.98(0.65-0.87)	0.002
Hypertension	4.19(1.76-11.98)	0.010	4.98(2.65-13.7)	0.003
Hypercholesterolemia	6.13(3.98-12.18)	0.003	5.98(4.01-13.12)	0.004
Diabetes	5.87(4.98-13.56)	0.003	6.76(3.93-12.87)	0.001
Obesity	5.87(2.01-3.87)	0.001	6.98(3.12-5.54)	0.002
Vitamin D	2.32(0.67-0.87)	0.013	-	-
Deficiency of Vit.D	-	-	2.65(1.65-4.87)	0.27

4. Discussion

Vitamin D deficiency is associated with coronary artery disease, and the actions of vitamin D are mediated by its binding to a specific nuclear Vitamin D receptor (VDR). VDRs are found in a variety of tissues including vascular smooth muscle cells, cardiomyocytes, and cells of the immune system [4, 5]. It has been found that one of the functions of calcitriol, as well as other VDR ligands, is to impede the proliferation of vascular smooth muscle cells. A number of extra-renal tissues, including vascular smooth muscle cells, produce the enzyme CYP27B1, which transforms the primary circulating form of vitamin D, calcidiol to its active form, calcitriol. Eventually, calcitriol reduces platelet aggregation and thrombogenesis, likely through the activation of the VDR.25,26 Today, the growth suppressant and immune-modulatory effects of calcitriol are of important interest because of their potential use in the management of disorders, including acute coronary syndrome(ACS) and atherosclerosis where the principal pathological mechanisms are unrestrained cell growth and remodeling in the vascular wall.25,30 Inflammation is also a key factor driving the processes of plaque formation, progression, and rupture in patients with ACS. An inflammatory subset of monocytes and macrophages has been reported to selectively concentrate in atherosclerotic plaques and produces pro-inflammatory cytokines. Calcitriol, involved in the regulation of body calcium homeostasis, promotes the differentiation of immature myeloid precursor cells into monocytes and macrophages. Crucially, calcitriol has long been shown to possess immune-regulatory properties and may inhibit key steps in this inflammatory process [3-5]. In present study 25-hyroxyvitamin D level is significantly lower in patient group compared with control group (17.4±8.9 vs. 28.8±21ng/mL). Vitamin D deficiency was present in 81.4% patient in case group whereas 57.7% in control group. Vitamin D deficiency was found to be an independent predictor of CAD after adjusting effect of other risk factors like hypertension, diabetes, smoking, obesity, high blood cholesterol and level of physical activity with adjusted odds ratio (95% confidence interval) 2.695 (1.148-

6.330). This observation was similar to study done by Verdoia *et al* who noticed in their study of 1484 patients that vitamin D deficiency was significantly associated with higher prevalence of CAD [adjusted OR (95%CI)=1.32(1.1-1.6), P=0.004] and severe CAD [adjusted OR (95%CI)=1.18(1-1.39), P=0.05].34 Similar observation was noticed in a study on 100 patients undergoing CAG done by Syal *et al* who found that the mean 25(OH) D level was 14.8±9.1ng/mL; vitamin D deficiency was present in 80% and only 7% had optimal 25(OH) D level.35 Raina *et al* also observed that CAD patients had significantly low 25-hyroxyvitamin D level than control (15.53 vs. 40.95ng/mL).36 They also observed that vitamin D level decreases among cases with age. The higher the age, the lesser is the vitamin D level. Seker *et al* observed in their study on 209 patients of stable CAD and 102 healthy control that vitamin D level of patient group is lower compared with control group 15.1±6.65 vs. 9.4±5.0ng/mL and vitamin D level is independently associated with extent and complexity of CAD assessed with SYNTAX scores (β=-0.396, $P<0.001$).37 Similarly Shanker *et al* reported that in 287 patients with CAD, vitamin D levels were significantly lower than in matched healthy controls, with patients in the first vitamin D quartile having a 2.54 times greater risk of CAD than those in the fourth quartile.38 More recently, Goleniewska *et al* evaluating 130 patients with ST-elevation myocardial infarction, identified vitamin D levels as independent predictors of multi vessel CAD at multiple stepwise logistic regression [9]. In present study 25-hyroxyvitamin D level was significantly lower in smokers than non-smoker ($p<0.001$) and 25-hyroxyvitamin D level was positively correlated with level of activities which was supported by other studies as well. In a study conducted by Brot *et al* it was observed that dietary vitamin D intake, non-smoking, and physical activity (in men) were significantly associated with higher concentrations of serum 25-hydroxyvitamin.40 In a study conducted by Rolim *et al* total cholesterol (β=−0.36, $p<0.01$) and BMI (β=−0.21, p=0.04) was independently associated with levels of 25-hydroxyvitamin D [4]. Like earlier studies negative relationship was found between body mass index, systolic blood pressure, total cholesterol, age and vitamin D level in present study. However this relationship unlike earlier studies was not found to be significant. This may be due to small sample size of study population.

5. Conclusion

Maintaining an optimal vitamin D serum level seems important not only for calcium homeostasis but also for cardiovascular risk, blood pressure control, prevalence of stroke, metabolic syndrome, and peripheral artery disease. Observational data support the link between vitamin D status and cardiovascular diseases, and vitamin D deficiency can be considered a cardiovascular risk marker. Vitamin D exerts its cardiovascular effects by reducing the activity of the renin-angiotensin-aldosterone system, lowering blood pressure values, and having an anti-inflammatory, antiproliferative, anti-hypertrophic, anti-fibrotic, antidiabetic, and antithrombotic effect and beneficial modulation of classical cardiovascular risk factors. Vitamin D deficiency is treatable and supplementation is inexpensive. Vitamin D could be combined with antihypertensive agents in order to control blood pressure, as a simple, inexpensive, and important prophylactic method in order to prevent cardiovascular morbidity, especially in the elderly. Even small gains in prevention are important from a public health perspective. CVDs remain the main cause of mortality in several countries worldwide. An understanding of the pathophysiological mechanisms involved, as well as their risk factors, is essential for planning of prevention and treatment strategies. In recent years, many studies have shown a relationship between vitamin D deficiency and CVDs, with a direct influence on prognosis. Based on the understanding of this association, the focus of researchers has been in the correction of vitamin deficiency with the aim of preventing diseases and improving the prognosis of established diseases. However, there are still no consistent data to recommend vitamin D replacement in the context of cardiac diseases. One point that deserves attention is the broad worldwide variation in the prevalence of vitamin D deficiency. Since endogenous vitamin D synthesis is dependent on solar exposure, which in turn varies according to latitude, perhaps the reference level for serum vitamin D also differs among countries depending on sunlight exposure. It is unclear whether the disappointment of the results of studies with vitamin D supplementation is due to an inability of the vitamin in exerting effects on established disease, or use of inappropriate supplementation doses. It is important to understand the doses required to maintain the serum levels of vitamin D above the desired level, as well as serial measurements of 25-hydroxyvitamin D with the aim of maintaining adequate levels of this vitamin during the entire follow-up duration.

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